



Inhalation or Instillation of Steroids for the Prevention of Bronchopulmonary Dysplasia

Bassler, Dirk

Abstract: Survival of extremely preterm infants has increased over recent years, but bronchopulmonary dysplasia (BPD) remains a major cause of morbidity. In the USA, BPD is the most common chronic respiratory disorder of infancy and affects the pulmonary and overall health of 10,000 preterm infants annually. Preclinical and clinical studies suggest a crucial role for lung inflammation and host immune response in the pathogenesis of BPD. Inflammation may result from, amongst others, chorioamnionitis, postnatal infection, ventilation, and the administration of oxygen. Infants with BPD have worse long-term outcomes than those without chronic lung disease. They are more than twice as likely to be readmitted to hospital in their first year of life and, having survived their primary hospitalizations, they are more likely to die than very preterm infants without chronic lung disease. Survivors with BPD have an increased risk of neurodevelopmental impairment and their respiratory function remains compromised well into adolescence. As the first generations of extremely low birth weight (ELBW) survivors have not yet reached retirement age, there are currently no reliable data addressing the association between BPD and pulmonary diseases of the elderly such as chronic obstructive pulmonary disease. Although BPD is quite common in ELBW infants, there are infants who do not develop BPD, which supports the argument that BPD is a preventable disease, emphasizing the need for high-quality safety and efficacy prevention studies. However, according to an Institute of Medicine statement regarding pediatric drug studies, the therapeutic area that has the fewest drugs indicated for neonates is BPD. As inflammation seems to be a primary mediator of injury in the pathogenesis of BPD, anti-inflammatory agents such as steroids have long been the focus of preventive research activities. However, systemic steroids, although reducing BPD, have frequently been linked to adverse neurodevelopmental outcomes and these considerations may have contributed to the recently reported widespread use of inhaled corticosteroids in neonatal units in North America and Europe. Inhaled corticosteroids were prescribed to 25% of infants born at <29 weeks of gestation with birth weights <1,500 g in neonatal units of 35 children's hospitals in the USA. According to a survey across all neonatal units in Germany, 46% administered inhaled corticosteroids to preterm infants either as prophylaxis or treatment for BPD [10]. Pediatricians and neonatologists should ask themselves whether the off-label use of inhaled corticosteroids in preterm infants is justifiable in view of the available evidence. The authors of the pertinent review from the Cochrane Collaboration, including 7 studies and 492 infants, conclude that there is currently no evidence to support the routine use of inhaled steroids for the prevention of BPD. Recently, the primary outcome results of the Neonatal European Study of Inhaled Steroids (NEUROSIS), including 863 very preterm infants (gestational age 23-27 weeks), have been presented at scientific conferences, but the full study report is not yet published. By contrast, intratracheal instillation of budesonide using surfactant as a vehicle has not yet become part of clinical practice. There are fewer studies addressing the risks and benefits of this mode of administration. In a randomized blinded pilot study in 116 very low birth weight infants who had severe radiographic respiratory distress syndrome and required mechanical ventilation shortly after birth, early intratracheal instillation of budesonide using surfactant as a vehicle resulted in significantly lower mean airway pressure on day 1 and day 3 and a significantly lower oxygen index and PCO₂ during the first 3 days compared with infants in the control group who had received surfactant without corticosteroids. More infants were extubated in the treatment group than in the controls at 1 and 2 weeks and the combined outcome of

death or chronic lung disease was significantly lower in the treatment group than in the control group (19 of 60 vs. 34 of 56). No clinically significant adverse effects were observed during the study and at the time of the follow-up assessment at 2-3 years of age. In the future, intratracheal instillation of budesonide using surfactant as a vehicle may play a role in the prevention of BPD in ELBW infants. However, before this therapy can be introduced into routine clinical care, remaining open questions need to be answered and appropriately powered studies need to be performed.

DOI: <https://doi.org/10.1159/000381132>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-112233>

Journal Article

Published Version

Originally published at:

Bassler, Dirk (2015). Inhalation or Instillation of Steroids for the Prevention of Bronchopulmonary Dysplasia. *Neonatology*, 107(4):358-359.

DOI: <https://doi.org/10.1159/000381132>

Inhalation or Instillation of Steroids for the Prevention of Bronchopulmonary Dysplasia

Dirk Bassler

Division of Neonatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Key Words

Bronchopulmonary dysplasia · Inhaled corticosteroids · Intratracheal instillation · Budesonide · Surfactant

Abstract

Survival of extremely preterm infants has increased over recent years, but bronchopulmonary dysplasia (BPD) remains a major cause of morbidity. In the USA, BPD is the most common chronic respiratory disorder of infancy and affects the pulmonary and overall health of 10,000 preterm infants annually [1]. Preclinical and clinical studies suggest a crucial role for lung inflammation and host immune response in the pathogenesis of BPD [2]. Inflammation may result from, amongst others, chorioamnionitis, postnatal infection, ventilation, and the administration of oxygen [2]. Infants with BPD have worse long-term outcomes than those without chronic lung disease. They are more than twice as likely to be readmitted to hospital in their first year of life and, having survived their primary hospitalizations, they are more likely to die than very preterm infants without chronic lung disease [3, 4]. Survivors with BPD have an increased risk of neurodevelopmental impairment [5] and their respiratory function remains compromised well into adolescence [6, 7]. As the first generations of extremely low birth weight (ELBW) survivors have not yet reached retirement age, there are currently no reliable data addressing the association between

BPD and pulmonary diseases of the elderly such as chronic obstructive pulmonary disease.

Although BPD is quite common in ELBW infants, there are infants who do not develop BPD, which supports the argument that BPD is a preventable disease, emphasizing the need for high-quality safety and efficacy prevention studies. However, according to an Institute of Medicine statement regarding pediatric drug studies, the therapeutic area that has the fewest drugs indicated for neonates is BPD [8]. As inflammation seems to be a primary mediator of injury in the pathogenesis of BPD, anti-inflammatory agents such as steroids have long been the focus of preventive research activities. However, systemic steroids, although reducing BPD, have frequently been linked to adverse neurodevelopmental outcomes and these considerations may have contributed to the recently reported widespread use of inhaled corticosteroids in neonatal units in North America and Europe. Inhaled corticosteroids were prescribed to 25% of infants born at <29 weeks of gestation with birth weights <1,500 g in neonatal units of 35 children's hospitals in the USA [9]. According to a survey across all neonatal units in Germany, 46% administered inhaled corticosteroids to preterm infants either as prophylaxis or treatment for BPD [10]. Pediatricians and neonatologists should ask themselves whether the off-label use of inhaled corticosteroids in preterm infants is justifiable in view of the available evidence. The authors of the pertinent review from the Cochrane Collaboration, includ-

ing 7 studies and 492 infants, conclude that there is currently no evidence to support the routine use of inhaled steroids for the prevention of BPD [11]. Recently, the primary outcome results of the Neonatal European Study of Inhaled Steroids (NEUROSIS), including 863 very preterm infants (gestational age 23–27 weeks), have been presented at scientific conferences, but the full study report is not yet published [12].

By contrast, intratracheal instillation of budesonide using surfactant as a vehicle has not yet become part of clinical practice. There are fewer studies addressing the risks and benefits of this mode of administration. In a randomized blinded pilot study in 116 very low birth weight infants who had severe radiographic respiratory distress syndrome and required mechanical ventilation shortly after birth, early intratracheal instillation of budesonide using surfactant as a vehicle resulted in significantly lower mean airway pressure on day 1 and day 3 and a significantly lower oxygen index and PCO₂ during the first 3 days compared with infants in the control group who had received surfactant without cortico-

steroids [13]. More infants were extubated in the treatment group than in the controls at 1 and 2 weeks and the combined outcome of death or chronic lung disease was significantly lower in the treatment group than in the control group (19 of 60 vs. 34 of 56). No clinically significant adverse effects were observed during the study and at the time of the follow-up assessment at 2–3 years of age [14]. In the future, intratracheal instillation of budesonide using surfactant as a vehicle may play a role in the prevention of BPD in ELBW infants. However, before this therapy can be introduced into routine clinical care, remaining open questions need to be answered and appropriately powered studies need to be performed.

© 2015 S. Karger AG, Basel

Disclosure Statement

The author is principal investigator of the Neonatal European Study of Inhaled Steroids (NEUROSIS), which is supported by the European Union (Grant Award HEALTH-F5-2009-223060).

References

- McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL: Bronchopulmonary dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. *Ann Am Thorac Soc* 2014;11(suppl 3):S146–S153.
- Wright CJ, Kirpalani H: Targeting inflammation to prevent bronchopulmonary dysplasia: can new insights be translated into therapies? *Pediatrics* 2011;128:111–126.
- Kugelman A, Reichman B, Chistyakov I, Boyko V, Levitski O, Lerner-Geva L, Riskin A, Bader D; Israel Neonatal Network: Postdischarge infant mortality among very low birth weight infants: a population-based study. *Pediatrics* 2007;120:e788–e794.
- Smith VC, Zupancic JA, McCormick MC, Croen LA, Greene J, Escobar GJ, Richardson DK: Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. *J Pediatr* 2004;144:799–803.
- Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators: Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003;289:1124–1129.
- Doyle LW; Victorian Infant Collaborative Study Group: Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–1992. *Pediatr Pulmonol* 2006;41:570–576.
- Vom Hove M, Prenzel F, Uhlig HH, Robel-Tillig E: Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. *J Pediatr* 2014;164:40–45.
- Beam KS, Aliaga S, Ahlfeld SK, Cohen-Wolkowicz M, Smith PB, Laughon MM: A systematic review of randomized controlled trials for the prevention of bronchopulmonary dysplasia in infants. *J Perinatol* 2014;34:705–710.
- Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR: Utilization of inhaled corticosteroids for infants with bronchopulmonary dysplasia. *PLoS One* 2014;9:e106838.
- Maas C, Poets CF, Bassler D: Survey of practices regarding utilization of inhaled steroids in 223 German neonatal units. *Neonatology* 2010;98:404–408.
- Shah V, Ohlsson A, Halliday HL, Dunn MS: Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. *Cochrane Database Syst Rev* 2012;5:CD001969.
- Bassler D, Halliday HL, Plavka R, Hallman M, Shinwell ES, Jarreau P-H, et al: The Neonatal European Study of Inhaled Steroids (NEUROSIS): an EU-funded international randomised controlled trial in preterm infants. *Neonatology* 2010;97:52–55.
- Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, Pyati S, Tsai CH: Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. *Pediatrics* 2008;121:e1310–e1318.
- Kuo HT, Lin HC, Tsai CH, Chou IC, Yeh TF: A follow-up study of preterm infants given budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants. *J Pediatr* 2010;156:537–541.